REMARKS

Formal Matters

Claims 1-9, 15-16, and 21-40 are pending after entry of the amendments set forth herein

Claims 10-14, and 17-20 have been canceled.

Claims 1-9, 15, and 16 were examined. Claims 1-9, 15, and 16 were rejected. No claims were allowed.

Claims 1-7, 9, 15, and 16 have been amended. Support for the amendments can be found in the claims as originally filed and throughout the specification at, for example: Claim 1: page 6, lines 6-8, and page 10, line 21 to page 11, line 4; Claim 2: page 10, line 21 to page 11, line 4; Claim 3: page 10, line 21 to page 11, line 4; Claim 4: page 11, line 36 to page 12, line 17; Claim 5: page 13, lines 6-17; Claim 6: page 13, lines 18-24; Claim 7: page 13, line 37 to page 14, lines 14; Claim 9: page 19, lines 26-33; Claim 15: page 24, lines 16-21; and Claim 16: page 37, lines 10-30.

The specification has been amended in the title and on pages 6, 33, 34, 35, 38, and 39 in order to address the Examiner's objections regarding sequence identification numbers and usage of trademarks.

New Claim 21-40 has been added. Support for new Claim 21-38 can be found in the claims as originally filed and throughout the specification at, for example,
Claim 21: original Claim 1 and page 9, line 33, through page 10, line 5; Claim 22: original Claim 2; Claim 23: original Claim 3; Claim 24: original Claim 4; Claim 25: page 12, lines 7-17; Claim 26: page 12, lines 7-17; Claim 27: page 10, lines 1-5; Claim 28: page 9, line 33, through page 10, line 1; Claim 29: page 9, line 33, through page 10, line 1; Claim 30: page 9, line 33, through page 10, line 1; Claim 31: page 16. lines 24-33; Claim 32: page 10, lines 4-5; Claim 33: Table 2, page 39 and 40; Claim 34: original Claim 5; Claim 35: original Claim 6; Claim 36: original Claim 7; Claim 37: original Claim 8; Claim 38: original Claim 9; Claim 39: original Claim 15; and Claim 40: original Claim 16.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

No new matter has been added.

Certification Regarding Sequence Listing

I hereby certify that the enclosed Sequence Listing is being submitted under 37 CFR §§ 1.821(c) and (e) in paper and computer readable form (Compact Disk labeled 'CRF').

As required by 37 CFR 1.821(f), I hereby state that the content of the paper and computer readable copy of the Sequence Listing, submitted in accordance with 37 C.F.R. §1.821(c) and (e) are the same. The Computer Readable Format (CRF), being submitted under 37 CFR §§ 1.52(e) and 1.824, is formatted on IBM-PC, the operating system compatibility is MS-Windows and the file listing is:

Seqlist.txt 35.9 KB created December 10, 2004.

I hereby certify that the enclosed submission includes no new matter. The Sequence Listing was prepared with the software FASTSEQ, and conforms to the Patent Office guidelines. Applicant respectfully submits that the subject application is in adherence to 37 CFR §§ 1.821-1.825.

Objections to the Specification

(a) Use of Trademarks (Office Action page 1)

The specification has been objected to for allegedly improperly using trademarks. The specification has been amended on pages 33, 34, 35, 38, and 39 in order to address the Examiner's objections regarding improper usage of trademarks. Accordingly, this objection may be withdrawn.

(b) Sequence Identifier (office Action page 2)

The specification has been objected to for disclosing a sequence on page 30 without a specific sequence identifier. The specification has been amended on page 38 in order to address the Examiner's objection. Accordingly, this objection may be withdrawn.

(c) Specification Page 6 (Office Action page 2)

The specification on page 6, line 32, has been objected to for a typographical error. The specification has been amended on page 6 to correct the error in syntax and to recite "as well as the **encoded** proteins". Accordingly, this objection may be withdrawn.

(d) Title (Office Action page 2

The title has been objected to for allegedly failing to describe the claimed invention. The title has been amended as suggested by the Examiner in the outstanding Office Action. Accordingly, this objection may be withdrawn.

Objections to the Claims

Claims 1-3 (Office Action page 2)

Claims 1-3 have been objected to because the species name in the claims is not italicized. Claims 1-3 have been amend to italicize *Cnidarian*. Accordingly, this rejection may be withdrawn.

Claim 4 (Office Action page 2)

Claim 4 has been objected to because the claim recited "residues" in association nucleic acid sequence instead of "nucleotides." Claim 4 has been amended to remove the objectionable language. Accordingly, this rejection may be withdrawn.

Claims 4, 6, 7, and 15-16 (Office Action page 2)

Claims 4, 6, 7, and 15-16 have been objected to because the claims recite "a nucleic acid". Claims 4, 6, 7, and 15-16 have has been amended to correct the antecedent issues raised by the Examiner. Accordingly, this rejection may be withdrawn.

Claim 9 (Office Action page 3)

Claim 9 has been objected to for reciting "and/or". Claim 9 has been amended to remove the objectionable language. Accordingly, this rejection may be withdrawn.

Rejection Under 35 U.S.C. § 101

Claims 1-9 and 15-16 have been rejected under 35 U.S.C. § 101 for allegedly reading on a product of nature. This rejection is respectfully traversed as applied and as it may be applied to the pending claims.

Claim 1 has been amended to recite "present in other than its natural environment." This phrase is defined in the specification, see page 6, lines 6-8, and clearly distinguishes the claimed compositions such that they do not read on a product of nature. As such, this rejection may be withdrawn.

Rejection Under 35 U.S.C. § 112, First Paragraph – Written Description

Claims 1-9, and 15-16 have been rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking written description. This rejection is respectfully traversed as applied and as it may be applied to the pending claims.

In making this rejection, the Examiner asserts on page 4 of the office action that "the claimed nucleic acid is only defined by a function (encoding a protein) not a structure". In addition, the Examiner also states that "the claims encompass mutations other than point mutations or single deletions which have not been described, therefore, the specification fails to provide a representative number of species for the claimed genus to show that applicant was in possession of the claimed genus" (Office Action, page 5).

The law is clear that, if a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if not every nuance of the claims is explicitly described in the specification, then the adequate written description requirement is met.[1] Further, "an applicant ...is

1 *In re Alton* 76 F.3d 1168, 37 USPQ2d 1578 (Fed. Cir. 1996).

generally allowed claims, when the art permits, which cover more than the specific embodiment shown."[2]

The Applicants maintain that the specification provides adequate written description support for such a disclosure. In particular, the Applicants respectfully submit that the specification provides abundant written description support for practicing the claimed invention. In particular, the Applicants note that the specification provides support for the subject nucleic acids at, for example, on page 8, line 6 through page 17, line 10; the particular non-aggregating aspect at, for example, on page 8, line 20 though page 9, line 32; exemplary methods of producing such mutants at, for example, on page 16, line 24, through page 17, line 5, and in greater detail on page 38, line 14 through page 39, line 22; resulting exemplary mutants at, for example, in Table 2 on page 39; constructs, vectors, expression cassettes, and expression systems including the subject nucleic acids at, for example, on page 13, line 37, through page 16, line 18; and applications using the subject non-aggregating mutants at, for example, on page 24, line 16, though page 37, line 6.

Moreover, the specification also provides abundant written description support for exemplary methods of evaluating protein aggregation in the in the examples section at, for example, page 40 and 41. Such exemplary methods include (1) pseudo-native protein electrophoresis (page 40), (2) light scattering (page 40), and (3) brightness in mammalian cell lines (page 41).

Furthermore the specification provides working examples demonstrating exemplary mutagenesis protocols for generating the subject nucleic acids encoding the non-aggregating proteins (Example II, page 38), examples of mutants generated (Example III, Table 2, page 39), and exemplary methods of evaluating protein aggregation suitable for use with the subject invention (Example IV, page 40).

In addition, with respect to DNA mutagenesis, the specification provides ample description of several protocols for site specific mutagenesis. See, for example, the following passage on pages 16 and 17:

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2 *Ethicon Endo-Surgery, Inc. v. United States Surgical Corp.*, 93 F.3d 1572, 40 USPQ2d 1019 (Fed. Cir. 1996).

Examples of protocols for site specific mutagenesis may be found in Gustin *et al. (1993)*, *Biotechniques* 14:22; Barany (1985), *Gene* 37:111-23; Colicelli *et al. (1985)*, *Mol. Gen. Genet.* 199:537-9; and Prentki *et al.* (1984), *Gene* 29:303-13. Methods for site specific mutagenesis can be found in Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, CSH Press 1989, pp. 15.3-15.108; Weiner *et al.* (1993), *Gene* 126:35-41; Sayers *et al.* (1992), *Biotechniques* 13:592-6; Jones and Winistorfer (1992), *Biotechniques* 12:528-30; Barton *et al.* (1990), *Nucleic Acids Res* 18:7349-55; Marotti and Tomich (1989), *Gene Anal. Tech.* 6:67-70; and Zhu (1989), *Anal Biochem* 177:120-4.

As noted by the Examiner in the Office Action, the pending claims are not limited to particular types of mutations, e.g., point mutations or single deletions, but encompass different types of mutations that result in a non-aggregating quality. The Applicants maintain that by showing specific examples of nucleic acids encoding non-aggregating mutants (Example III, Table 2, page 39), and well as providing a thorough description of DNA mutagenesis methods suitable for use with the present application (pages 16-17), the Applicants have provided adequate written descriptive support for the scope of the claims.

In view of the above, it is submitted that the claims do comply with the written description requirement in that the claims are directed to nucleic acids encoding non-aggregating chromo- or fluorescent mutant proteins of an aggregating *Cnidarian* chromo- or fluorescent protein or mutant thereof. The specification provides multiple representative examples, including working examples of representative nucleic acids encoding exemplary mutant non-aggregating proteins, such that one of skill in the art would have no doubt that the applicant was in possession of the invention as claimed at the time the application was filed.

Rejection Under 35 U.S.C. § 112, First Paragraph – Enablement

Claims 1-9 and 15-16 have been rejected under 35 U.S.C. § 112, first paragraph, for allegedly not providing enablement for any non-aggregating mutant or any aggregating mutant thereof or any nucleic acid fragment or any application employing the nucleic acid. In view of the remarks made herein, this rejection is respectfully traversed as applied and as it may be applied to the pending claims.

As noted in the Office Action, a specification complies with the statute even if a reasonable amount of experimentation is required, as long as the experimentation is not "undue". One way to determine if undue experimentation is required is to utilize the *Wands* factors: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." All of the factors need not be reviewed when determining whether a disclosure is enabling.[3]

The Applicants respectfully submit that when evaluated in view of the relevant *Wands* factors, the specification clearly enables one of skill in the art to practice the subject invention without undue experimentation. In other words, Claims 1-9 and 15-16 contain subject matter which is adequately described in the specification in such a way to teach someone how to make and use the claimed invention without having to practice undue experimentation. An analysis of the relevant *Wands* factors is provided below.

(1) the quantity of experimentation necessary

The Applicants respectfully submit that the quantity of experimentation required to practice the subject invention is reasonable. The courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP §2164.01.[4] As the court explained:

> [A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.[5]

Practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation

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3 See *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991).
4. See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom.*, *Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).

where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example, the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art which routinely performs such long experiments.

> The claimed compositions recite isolated polypeptides with 60% or more sequence identity to SEQ ID NO:3 that suppress proliferation of lympho-hematopoietic cells. The only experiments, if any, that need be performed to enable the entire scope of the claim are those designed to determine which sequences retain the ability to suppress proliferation of lympho-hematopoietic cells. The sequence of polypeptides retaining biological activity is determined through routine experimentation that is empirical in nature, typically employing nothing more than performing the same assay disclosed in the specification on a variety of sequence variants of the polypeptide made by routine recombinant DNA techniques. Since these experiments are empirical in nature, no undue experimentation is required. In other words, the only experimentation that may be required to enable the claimed invention are those experiments to determine the presence of a certain activity, and since this only requires a routine assay on polypeptide variants to determine the active variants, no undue experimentation is necessary.[6]

The claims of present application are directed to nucleic acids present in other than their natural environment that encode non-aggregating chromo- or fluorescent mutant of an aggregating *Cnidarian* chromo- or fluorescent protein or mutants thereof. As provided below, the Applicants maintain that the specification provides ample disclosure to enable one skilled in the art to practice the claimed invention. For example, the subject nucleic acids are described, for example, on page 8, line 6 through page 17, line 10; the particular non-aggregating aspect is described, for example, on page 8, line 20 though page 9, line 32; exemplary methods of producing such mutants are described, for example, on page 16, line 24, through page 17, line 5, and in greater detail on page 38, line 14 through page 39, line 22; resulting exemplary mutants are described at, for example, in Table 2 on page 39; constructs, vectors, expression

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5. *In re Wands* 8 USPQ 2d at 1404.
6. *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986)

cassettes, and expression systems including the subject nucleic acids are described, for example, on page 13, line 37, through page 16, line 18; and applications using the subject non-aggregating mutants are described, for example, on page 24, line 16, though page 37, line 6. Therefore, in view of such guidance provided in the specification, in combination with the knowledge of one of skill in the art, and experimentation that may be necessary is reasonable.

The Examiner also stresses that "the 'so called manner sufficient to produce a non-aggregating mutant' is not discussed" (Office Action, page 19). The Examiner notes that "on pages 8-9 decreased aggregation is discussed, however, the instant specification does not set forth for example, the specific environment such as the solution needed to achieve the properties claimed" (Office Action, page 9). The applicants respectfully disagree. In particular, the Applicants note that the specification on pages 8 provides the following conditions:

> Any of a wide variety of buffer systems used in the art to study physiological phenomena can be used for *in vitro* comparisons. Non-limiting examples of such conditions include, but are not limited to, a salt concentration in the range of from about 0.01 mM to about 0.1 mM; a temperature in the range of from about 19°C to about 25°C; and a pH in the range of from about 6.5 to about 8.0. Buffers that are suitable for comparison of aggregation include, but are not limited to, any physiological buffer; Tris-Cl, phosphate buffered saline; Tris buffered saline; borate buffered saline; and the like. An example is 1 × Tris-Cl buffer, pH 8.8, 0.1% SDS, room temperature.

In addition, the specification on page 9 also provides the following methods of measuring the degree of aggregation that suitable for use with the subject invention:

> Methods of measuring the degree of aggregation are known in the art; any known method can be used to determine whether a given mutant shows a reduction in aggregation compared to corresponding aggregating analogue, e.g., when compared to a corresponding aggregating wild type polypeptide. Such methods include, but are not limited to, "pseudo-native" protein gel electrophoresis, as described in the Examples; gel filtration; ultracentrifugation; circular dichroism; and light scattering. Aggregation can be measured by light scattering, as described in the Examples. For non-aggregated proteins, the ratio of absorption at a shorter wavelength to the absorption at a longer

> wavelength is close to zero. In some embodiments, the ratio of absorption at 400 nm to the absorption at 566 nm of a non-aggregating polypeptide is in the range of from about 0.01 to about 0.1, from about 0.015 to about 0.09, from about 0.02 to about 0.08, from about 0.025 to about 0.07, or from about 0.03 to about 0.06.

Moreover, exemplary methods of evaluating protein aggregation are further discussed in the examples section at, for example, page 40 and 41. Such exemplary methods include (1) pseudo-native protein electrophoresis (page 40), (2) light scattering (page 40), and (3) brightness in mammalian cell lines (page 41). Accordingly, for at least the reasons noted above, the specification provides adequate enablement for determination of a non-aggregating property. Furthermore, since the knowledge in the relevant field of DNA mutagenesis and protein screening is high, the technical concerns raised by the Examiner could be readily addressed by one of skill in the art without undue and excessive experimentation.

Moreover, the Examiner further notes that the "the claims recite the use of the nucleic acid in an application (see for example claim 15), however, there is no limitation as to what type of application is intended by the claimed invention, which is not supported by the instant specification" (Office Action, page 10). The applicants respectfully disagree. In support, the Applicants draw the Examiner's attention to various sections of the specification in which several exemplary applications the subject nucleic acids are suitable for use with. In particular, the specification on pages 15 and 16 provides details for using the subject nucleic acids in producing expression systems, such as bacteria, yeast, and mammalian cells. In addition, the specification on pages 22 through 24 provides details for use of the subject nucleic acids to generate transgenic, non-human plants and animals. Furthermore, the specification on pages 24 through 37 provides details for using the subject non-aggregating mutant proteins in various applications, including for example: (1) fluorescence resonance energy transfer protocols (specification, page 25), (2) bioluminescence resonance energy transfer protocols (specification, page 26), (3) use as biosensors in prokaryotic and eukaryotic cells (specification, page 27), (4) applications involving the automated screening of arrays of cells expressing fluorescent reporting groups by using microscopic imaging and electronic analysis (specification, page 28); (5) use in high through-put screening

assays (specification, page 29); (6) in vivo makers in animals (specification, page 29), as well as a variety of other applications further detailed in the specification.

Accordingly, the Applicants respectfully submit that the specification and the amended claims, coupled with the information available in the relevant art, one of skill would be able to practice the claimed invention without undue and excessive experimentation.

(2) the amount of direction or guidance presented

The claims of the present invention are directed to nucleic acids present in other than their natural environment and encoding non-aggregating chromo- or fluorescent mutants of aggregating *Cnidarian* chromo- or fluorescent proteins or mutants thereof. As noted above, the specification provides ample support for such recitations, for example at page 8, line 6 through page 17, line 10, with the particular non-aggregating aspect is described, for example, on page 8, line 20 though page 9, line 32.

Moreover, exemplary methods of producing such mutants are described, for example, on page 16, line 24, through page 17, line 5, and in greater detail on page 38, line 14 through page 39, line 2213-16 and pages 19-22. Finally, the specification also provides abundant description for methods of evaluating protein aggregation on page 9 as well as in the examples section at, for example, page 40 and 41. Such exemplary methods include (1) pseudo-native protein electrophoresis (page 40), (2) light scattering (page 40), and (3) brightness in mammalian cell lines (page 41).

Accordingly, for at least the reasons described above, the Applicants respectfully submit that the specification provides ample guidance and direction to the practice the claimed invention.

(3) the presence or absence of working examples

Compliance with the enablement requirement under Title 35 U.S.C. §112, first paragraph does not require or mandate that a specific example be disclosed. The specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice the invention

without undue experimentation.[7] Furthermore, "[n]othing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples."[8]

The present application does contain working examples demonstrating exemplary mutagenesis protocols for generating the subject nucleic acids encoding the non-aggregating proteins (Example II, page 38), examples of mutants generated (Example III, Table 2, page 39), and exemplary methods of evaluating protein aggregation suitable for use with the subject invention (Example IV, page 40). As such, the present application does provide a person skilled in the art, through the specification as well as the working example, sufficient enablement for the subject invention.

Moreover, the Applicants note that the presence or absence of working examples is but one factor to be taken into consideration in determining whether the specification is enabling for the full scope of the claims. Under MPEP § 2164.02 the consideration is whether one skilled in the art would be expected to be able to extrapolate the provided examples across the entire scope of the claim. As presented herein, Applicants argue that it would be reasonable to conclude that one skilled in the art would be able to extrapolate the working examples provided in the specification across the across the entire scope of the claims without excessive and undue experimentation. As such, based on the disclosure provided in the application one skilled in the art would be able to extrapolate the working examples to the full scope of the pending claims.

(4) the nature of the invention

The nature of the invention is generally directed towards nucleic acids encoding non-aggregating chromo- or fluorescent mutants of an aggregating *Cnidarian* chromo- of fluorescent protein or mutant thereof. Therefore, such methods may generally encompass DNA manipulation and specifically DNA mutagenesis or biochemical reactions with respect to DNA and proteins. As such, the nature of the invention typically involves experimental research that may include manipulation and/or analyzing biomolecular components. Accordingly, the nature of the invention is that practitioners

7. *In re Borkowski*, 164 USPQ at 645.
8. *In re Robins* 166 USPQ 552 at 555 (CCPA 1970).

of this art are prepared to perform experimental research. As such, when viewed in light of the ample guidance provided by the specification, the state of the art, the high relative skill of those in the art, etc., the amount of experimentation, if any, needed to practice the subject invention is not excessive.

(5) the state of the prior art

The subject invention is concerned with nucleic acids encoding non-aggregating chromo- or fluorescent mutant proteins. Accordingly, the subject invention relates to DNA manipulation in general and specifically DNA mutagenesis and biochemical reactions involving DNA and proteins. As noted above the state of the art with respect to DNA mutagenesis and protein characterization is sufficiently well developed as evidenced by the numerous publications and issued patents in the relevant filed. As such, the Applicants maintain that the state of the art is well developed such that one skilled in the art would be able to readily address any technical concerns.

(6) the relative skill of those in the art

There is a high level of skill of those in the art who practice the present invention. Typically, practitioners of the art of nucleic acid manipulation are highly skilled in fields such as the biological and biochemical sciences and the like and typically possess advanced degrees. Accordingly, one skilled in the relevant art would be capable of addressing the technical concerns that the Examiner specifically raised in the Office Action.

(7) the predictability or unpredictability in the art

The subject invention is concerned with DNA manipulation, nucleic acid expression, and protein characterization. As such, the subject invention pertains to the fields of DNA manipulation, nucleic acid expression, and protein characterization, the art of which is not as unpredictable as the Examiner asserts.

The Applicants note that the field of DNA mutagenesis is sufficiently well developed; therefore it is not an unpredictable art. For example, as provided in the specification, the Applicants note that several protocols for site specific mutagenesis

were well known at the time the present application was filed. See, for example, the following passage on pages 16 and 17:

> Examples of protocols for site specific mutagenesis may be found in Gustin *et al. (1993)*, *Biotechniques* 14:22; Barany (1985), *Gene* 37:111-23; Colicelli *et al. (1985)*, *Mol. Gen. Genet.* 199:537-9; and Prentki *et al.* (1984), *Gene* 29:303-13. Methods for site specific mutagenesis can be found in Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, CSH Press 1989, pp. 15.3-15.108; Weiner *et al.* (1993), *Gene* 126:35-41; Sayers *et al.* (1992), *Biotechniques* 13:592-6; Jones and Winistorfer (1992), *Biotechniques* 12:528-30; Barton *et al.* (1990), *Nucleic Acids Res* 18:7349-55; Marotti and Tomich (1989), *Gene Anal. Tech.* 6:67-70; and Zhu (1989), *Anal Biochem* 177:120-4.

Moreover, by reporting examples of such nucleic acids encoding non-aggregating mutant proteins, the Applicants maintain that the field is not as unpredictable as asserted by the Examiner. In sum, armed with the teachings provided in the specification, the Applicants stress that the field is not so unpredictable. One could practice the full scope of the claimed invention without undue experimentation.

(8) the breadth of the claims

The claims of the instant application encompass nucleic acids encoding non-aggregating chromo- or fluorescent mutants of an aggregating *Cnidarian* chromo- of fluorescent protein or mutant thereof. As noted above, the specification provides ample support for such recitations, for example at pages 8-17 and pages 38-44. As such, the specification provides the requisite enablement for a person of skill in the art to make and practice the invention to the full scope of the pending claims.

In sum, the amount of experimentation required to subject invention would not be undue and excessive because working examples have been provided, guidance is given on how to generate such nucleic acids, and one of skill in the art would be able to perform the experiments as a matter of routine. The specification therefore provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation. Accordingly, the specification clearly enables the subject invention as demonstrated in view of the relevant *Wands* factors.

As such, for at least the reasons described above, Claims 1-9 and 15-16 are adequately enabled by the specification. Accordingly, the Applicants respectfully request that the rejection of Claims 1-9 and 15-16 under 35 U.S.C. §112, first paragraph be withdrawn.

Rejection Under Obvious-Type Double Patenting

Application No. 10/006,922 (Office Action, page 16)

Claims 1-3, 5-8 and 16 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-5, 8-10, 12-15, 16, 17, 20, 21, 22-23, and 31 of co-pending Application No. 10/006,922. This rejection is respectfully traversed as applied and as it may be applied to the pending claims.

As noted above, the claims of the present application are directed to nucleic acids encoding **non-aggregating** chromo- or fluorescent mutants of an aggregating *Cnidarian* chromo- of fluorescent protein or mutant thereof. The specification on page 8, specifically notes that following:

> By non-aggregating is meant that the proteins do not aggregate, i.e. complex with each other form high molecular weight aggregates. As used herein, an "aggregate" refers to a higher order molecular complex, e.g., a complex that comprises two or more tetramers of the protein. The molecular weight of such aggregates typically exceeds about 100 kDa, and more typically about 150 kDa. Aggregates are distinguished from mulitimers, where the term "multimer" refers to oligomers, such as dimers, trimers, and tetramers. Non-aggregating polypeptides of the subject invention include polypeptides that show reduced aggregation in vitro and/or in vivo as compared to their corresponding aggregating analogues, e.g., corresponding wild type proteins.

In contrast, co-pending '922 application is directed to nucleic acids encoding chromo- or fluorescent protein from non-bioluminescent *Cnidarian* species. The cited reference is silent as to mutant chromo- or fluorescent proteins that possess a decreased or non-aggregating quality from *Cnidarian* species.

As set out in MPEP § 804 (see section II. B. 1.), in determining whether a nonstatutory basis exists for a double patenting rejection, the first question to be asked is - does any claim in the application define an invention that is merely an obvious

variation of an invention claimed in the cited patent or application? An "obviousness-type" nonstatutory double patenting rejection might be appropriate only when the answer is "yes". A double patenting rejection of the obviousness-type is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. § 103" except that the patent principally underlying the double patenting rejection is not considered prior art.[9] Therefore, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a § 103 obviousness determination.[10]

Moreover, MPEP § 2144.08 (II) states the following:

> The patentability of a claim to a specific compound or subgenus embraced by a prior art genus should be analyzed no differently than any other claim for purposes of 35 U.S.C. 103.
>
> ...
>
> The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994)

As such, while the scope of the claims of the cited reference are directed to a broad genus of nucleic acids that may encompass non-aggregating species, claims directed to the narrower non-aggregating species are patentable within the broader genus. Therefore, the Applicants respectfully request that this rejection be withdrawn.

Application No. 10/845,484 (Office Action, page 18)

Claims 1-3, 5-8 and 15-16 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-4, 10-14, and 19-20 of co-pending Application No. 10/845,484. This rejection is respectfully traversed as applied and as it may be applied to the pending claims.

9*In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967).

10 *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). As summarized at MPEP § 804, the factual inquiries are as follows:

(A) Determine the scope and content of a patent claim and the prior art relative to a claim in the application at issue;
(B) Determine the differences between the scope and content of the patent claim and the prior art as determined in (A) and the claim in the application at issue;
(C) Determine the level of ordinary skill in the pertinent art; and
(D) Evaluate any objective indicia of nonobviousness.

However, the Applicants respectfully disagree. As noted above, the claims of the present application are directed to nucleic acids encoding **non-aggregating** chromo- or fluorescent mutants of an aggregating *Cnidarian* chromo- of fluorescent protein or mutant thereof.

In contrast, co-pending '484 application is directed to nucleic acids encoding interconverted mutant chromo- or fluorescent proteins, as well as the polypeptides.

Accordingly, for the same reasons noted above, while the scope of the claims of the cited reference are directed to a broad genus of nucleic acids that may encompass non-aggregating species, claims directed to the narrower non-aggregating species are patentable within the broader genus. Therefore, the Applicants respectfully request that this rejection be withdrawn.

Application No. 10/806,930 (Office Action, page 20)

Claims 1-3, 5-8 and 16 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-5, 7-10, and 17 of co-pending Application No. 10/806,930. This rejection is respectfully traversed as applied and as it may be applied to the pending claims.

However, the Applicants respectfully disagree. As noted above, the claims of the present application are directed to nucleic acids encoding **non-aggregating** chromo- or fluorescent mutants of an aggregating *Cnidarian* chromo- of fluorescent protein or mutant thereof.

In contrast, co-pending '484 application is directed to nucleic acids encoding a polypeptide product comprising a first and second chromo/fluorescent domain, optionally joined by a linking domain, wherein the first and second chromo/fluorescent domains associate with each other under intracellular conditions so that the encoded polypeptide assumes a tertiary structure.

Accordingly, for the same reasons noted above, while the scope of the claims of the cited reference are directed to a broad genus of nucleic acids that may encompass non-aggregating species, claims directed to the narrower non-aggregating species are patentable within the broader genus. Therefore, the Applicants respectfully request that this rejection be withdrawn.

Conclusion

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Dec. 21, 2004

By: _____
Edward J. Baba
Registration No. 52,581

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, CA 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

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